SSBP Syndrome Sheets

Neurofibromatosis Type 1 (NF1)

Genetics

Autosomal dominant. Gene localised to 17q11.2. The gene product (neurofibromin) regulates the RAS-MAPK signaling pathway and is thought to suppress tumour formation by regulating cell division (Tidyman, 2009). A high spontaneous mutation rate means that about half of all cases arise in unaffected families.

Incidence/prevalence

About 1 in 2,700 births.

Diagnosis

In those people who do not have a parent with NF1, two of the following must be present to meet diagnostic criteria: (a) 6 or more café au lait macules (>5mm pre-pubertal, >15 mm post-pubertal), (b) axillary or inguinal freckling, (c) two or more neurofibromas of any type, or one plexiform neurofibroma, (d) optic pathway glioma, (e) two or more Lisch nodules, or choroidal abnormalities, (f) a distinctive osseous lesion, (g) a heterozygous pathogenic NF1 variant, with a variant allele fraction of 50% in apparently normal tissue

In those people who have a parent with NF1, diagnostic criteria are met if one or more features above are present (Legius, Messiaen L, et al 2021).

Physical features

Physical manifestations of NF1 include café-au-lait spots, which occur in the first few years of life, intertriginous freckling, Lisch nodules (i.e. pigmented iris hamartomas or freckling in the iris), neurofibromas (i.e. benign Schwann cell tumors, divided into four types: (1) focal or diffuse cutaneous, (2) subcutaneous (under the skin), (3) spinal, and (4) nodular or diffuse plexiform neurofibromas, which develop from nerves and extend into surrounding structures, and which can transform into malignant tumours), optic pathway gliomas, and distinctive bone lesions (e.g., short stature or dystrophic scoliosis). Macrocephaly is common (Huijbregts, 2011).

Life expectancy

For most people with NF1 life expectancy is normal. However, the nature and severity of clinical features may change prognosis.

Brain abnormalities

Magnetic Resonance Imaging studies revealed many different abnormalities in the brains of NF1-patients. These include T2-hyperintensities (of which the nature is not yet known, and which do not seem to have clinical implications), volumetric abnormalities (mainly enlargements of subcortical structures), white matter abnormalities and differences in functional connectivity. The last three appear to be related to cognitive and social outcomes. The lifetime prevalence of epilepsy is reported to be 5.4%. (Bernando, 2020)

Behavioural characteristics

Many patients experience social and behavioural difficulties (Barton & North, 2004). These include communication difficulties and difficulties forming and maintaining friendships. Approximately 25% of children with NF1 meet the diagnostic criteria for autism, and another 25-30% exhibit the broader autistic phenotype (Chisholm, 2022). There is emerging evidence that the autism phenotype in NF1 is more homogenous than idiopathic autism, with reduced restrictive and repetitive behaviours compared to socio-communication difficulties. Cognitive deficits partly underlie the social dysfunction observed in NF1 (Huijbregts & De Sonneville, 2011). ADHD has been reported in 40—50% (Payne, 2021).

Cognitive characteristics

The global intellectual abilities of individuals with NF1 fall within a normal distribution, albeit towards the lower end of this distribution. More than half of children with NF1 show significant scholastic difficulties. Specific cognitive deficits occur in up to 80% of people with NF1, with attention, executive function and visual perception particularly affected

Treatment

People with NF1 should be reviewed at least annually and usually require multi-disciplinary care. Monitoring skin and bone changes (scoliosis) are important.
Because of the multi-faceted nature of NF1, treatment is generally aimed at specific symptoms. For example, optic glioma are most often treated with chemotherapy (Ardern-Holmes & North, 2011). Also, trials have been performed with bisphosphonate drugs to treat bone abnormalities (Heervä et al., 2014), whilst results of studies using statins to treat social and cognitive impairments were inconclusive at best (Payne et al., 2016; Stivaros et al., 2018; Van der Vaart et al., 2013). Anti-seizure medications are used to treat epilepsy.
Methylphenidate does seem to ameliorate some of the cognitive symptoms associated with NF1. Trials are currently underway with new medication (Lamotrigine) to improve cognitive and social functioning via increase of interneuron excitability (Omrani et al., 2015). To date, relatively little attention has been given to non-pharmaceutical interventions, whereas those that have been performed seem to have been relatively successful (e.g. Arnold et al., 2016).

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